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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/982,586	10/17/2001	George A. Gaitanaris	50001/002005	7567

21559 7590 07/02/2003

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EXAMINER	
QIAN, CELINE X	

ART UNIT	PAPER NUMBER
1636	6

DATE MAILED: 07/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/982,586	GAITANARIS, GEORGE A.	
	Examiner	Art Unit	
	Celine X Qian	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) *15-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1-17 are pending in the application.

Election/Restrictions

Applicant's election without traverse of Group I in Paper No. 5 is acknowledged.

Accordingly, claims 15-17 are withdrawn from consideration for being directed to non-elected subject matter. Claims 1-14 are currently under examination.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
The oath or declaration is directed to the specification of application 09/002,046 instead of the current application. A substitute copy of oath and declaration is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement

and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the relative skill of those in the art; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue" (MPEP 2164.01 (a)).

The nature of the invention is a mouse comprising a transgene comprising a regulatory gene encoding a regulatory protein, a transcription terminator, wherein the transgene has integrated into an endogenous gene of said mouse such that the regulatory gene is under the control of the promoter of said endogenous gene, wherein the terminator mutagenizes said endogenous gene.

The breadth of the claims is very broad. The broadest claim encompasses a transgenic mouse comprising insertion of any regulatory protein with transcription terminator at any site of the genome. Further, the claims encompass such a transgenic mouse with any phenotype or no phenotype.

The teaching of the specification is limited. The invention is based on insertional mutagenesis of ES cells and producing mosaic mice. The specification only teaches a method of create mutation in mouse genome by random insertion of retroviral vector comprising a gene encoding regulatory protein into mouse ES cells. However, there is no evidence nor guidance as to what will be the characteristics or phenotype of the mice. There specification also fails to teach how to use the mice with claimed genotype but without any phenotype. Therefore, one skilled in the art would not know how to use the invention.

State of the Art, Predictability or Unpredictability of the art, Amount of experimentation necessary and Skill level of the artisan: When considering the predictability of this invention, one has to remember that many of the phenotypes examined in transgenic and knockout models are influenced by the genetic background in which they are studied and the effect of allelic variation and the interaction between the allelic variants (pg.1425, paragraph 1 in Sigmund, C.D. 2000. Arterioscler Thromb Vasc Biol.20:1425-1429). Friedman et al. teach that 15 out of 24 strains of transgenic mouse generated by random insertion of a b-gal neo fusion do not exhibit an overt phenotype when bred to homozygosity (see page 1521, 1st col., 2nd paragraph, lines 1-2). The specification does not disclose any phenotype of the mouse comprising random gene mutation. It is unpredictable which specific gene would be mutagenized and what specific phenotype would result from such mutation. Thus, the specification, in the instant case, is not enabling for transgenic and/or knock out mouse that exhibit no phenotype.

In view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, one skilled in the art would have to engage in undue experimentation to use the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "another gene" renders the claim indefinite because it is unclear whether it is referring to an endogenous gene or another transgene.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-8 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Friedrich et al. (IDS), in view of St-Onge et al (1996, Nucleic Acid Research, Vol.24, No.19, pp.3875-3877).

Friedrich et al. teach a transgenic mouse comprising in its genome a transgene comprising a fusion of β-gal and neomycin phosphotransferase gene under the control of a promoter of an endogenous gene (see page 1514, 1st col., 2nd paragraph and Figure1), wherein the fusion gene is placed downstream of a splice acceptor sequence (see page 1514, 1st col., 3rd paragraph and Figure 1). Friedrich et al. also teach the transgene further comprises retroviral packaging and integration sequences isolated from a moloney murine leukemia virus (see page 1521, 2nd col., 1st paragraph). However, Friedrich et al. do not teach that the transgene comprising a gene encoding a regulatory protein.

St-Onge et al. teach a method of temporal control of the Cre recombinase in transgenic mice by a tetracycline responsive promoter (see abstract). St-Onge et al. teach a transgenic mouse comprising in its genome a transgene encoding a tetracycline repressor (tetR) and the

VP16 from herpes simplex virus (see page 3875, 1st col., 1st paragraph). St-Onge et al. also teach a transgenic mouse comprising a Cre recombinase gene under the control of CMV promoter that contains a tet-operator (tetO) sequence (see page 3875, 1st col., 1st paragraph). St-Onge et al. also teach a transgenic mouse comprising a reporter construct in which the CMV promoter and a β-gal gene are separated by transcriptional stop sequences flanked by two lox P sites (see page 3875, 1st col., 1st paragraph and Figure 1). St-Onge further teach that mating of the three transgenic lines to generate mice comprising all three transgenes, wherein said triple transgenic mice results in Cre mediated excision of the stop sequence and generation of the reporter gene signal (see page 3875, 1st col., 2nd paragraph, and Figure 2A). St-Onge et al. further teach that treating said Cre-tetR transgenic mice with tetracycline and subsequent mating to the transgenic mice comprising the reporter construct does not result in reporter expression (see page 3876, 2nd col., and Figure 3A).

It would have been obvious to one of ordinary skill of art to add a gene encoding a regulatory protein such as fusion of tetR and VP16 to the transgene taught by the Friedrich et al. based on the combined teaching of Friedrich et al. and St-Onge et al. The ordinary skilled artisan would have been motivated to do so to provide the temporal control of another gene in the transgenic mouse as taught by St-Onge et al. The level of skill in the art of molecular cloning is high. Absent evidence to the contrary, one of ordinary skill of the art would have reasonable expectation of success to make a transgenic mouse comprising a transgene comprising a regulatory protein under the control of an endogenous promoter as claimed. Therefore, the invention would have been prima facie obvious to one of ordinary skill of art at the time the invention was made.

Claims 9-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Friedrich et al., in view of St-Onge et al. as applied to claims 1-8 and 14 above, and further in view of Zhang et al (1996, BBRC, vol.227, pages 707-711).

The teaching of Friedrich et al. and St-Onge et al. were discussed above. However, Friedrich et al. and St-Onge et al. do not teach a marker protein as a fusion protein of a green fluorescent protein and neomycin phosphotransferase.

Zhang et al. teach several reporter genes, such as secreted alkaline phosphatase, B-gal, firefly luciferase, CAT and GFP can be used in *in vivo* reporter assays (see page 707, 3rd paragraph). Zhang et al. further teach that GFP is an important reporter because it has advantages over other reporter for not requiring additional cofactors, substrates, or additional gene products. Zhang et al. further teach the generation of a humanized EGFP that has great sensitivity and stability (see bridging paragraph of 708 and 709).

The obviousness for making a transgenic mouse as comprising a transgene which encodes a regulatory protein under the control of an endogenous gene promoter was discussed above. It would have been obvious to one of ordinary skill in the art to replace the β-gal marker protein with GFP based on the teaching of Zhang et al. The ordinary skilled artisan would have been motivated to do so because GFP signal can be observed directed without additional staining or enzymatic reaction. The level of skill in the art is high. Absent evidence from the contrary, one of ordinary skill in the art would have reasonable expectation of success to make a transgenic mouse as comprising a regulatory protein under the control of an endogenous promoter and further comprise a GFP and neomycin phosphotransferase fusion protein as a

marker. Therefore, the invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Friedrich et al., in view of St-Onge et al. as applied to claims 1-8 and 14 above, and further in view of Bremer et al.

The teaching of Friedrich et al. and St-Onge et al. were discussed above. However, Friedrich et al. and St-Onge et al. do not teach the transgene further comprises a recognition sequence recognized by a yeast VDE DNA endonuclease.

Bremer et al. teach a VDE endonuclease from *Saccharomyces crevisiae* and further teach that the VDE cleavage sites can uniquely mark specific genome locations.

The obviousness for making a transgenic mouse as comprising a transgene which encodes a regulatory protein under the control of an endogenous gene promoter was discussed above. It would have been obvious to an ordinary skilled artisan to insert VDE recognition sites into the transgene because St-Onge et al. has demonstrated an example of temporal regulation of gene expression by Cre-lox P mediated recombination in transgenic mouse. VDE recombinase system is just another way to regulate transgene expression in mouse. One of ordinary skill in the art would have been motivated to insert the VDE recognition sites into the transgene to achieve temporal regulation of the transgene expression. The level of skill in the art is high. Absent evidence to the contrary, one of ordinary skill in the art would have reasonable expectation to insert VDE recombinase recognition sites to the transgene. Therefore, the invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 703-306-0283. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Celine Qian, Ph.D.
June 25, 2003

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER